

بسم الله الرحمن الرحيم

**THE EFFECT OF FEEDING *CORIANDRUM SATIVUM*
(KUZBARA) FRUITS POWDER ON PLASMA LIPIDS
PROFILE IN CHOLESTEROL FED RATS**

By

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A thesis submitted to the University of Khartoum in partial
fulfillment for the requirement of degree of
Master of Science in Biochemistry

Department of Biochemistry
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May, 2007

DEDICATION

*To the soul of my father
To my mother
To my beloved family,
To my darlings and friends*

With respect

Shihab Eldin

ACKNOWLEDGEMENTS

Praise is to *Allah*, the Lord of the creation who granted me every thing including the mind, health and patience to accomplish this work.

Special thanks and appreciation to my supervisor Dr. **Barakat El Hussein Mohamed** for his guidance, valuable advices, suggestions and kind supervision throughout the study period.

My deepest gratitude to the staff member of Research and Laboratory Unit, Khartoum Teaching Hospital for laboratory facilities.

Thanks to Mr. Hamza Ibrahim for his patience and typing of the thesis.

The endless thanks are due to my friend Maha Mohamed Khalil for her support and encouragement.

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ABSTRACT

The aim of this study was to investigate the effect of *Coriandrum sativum* fruits powder on plasma total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), triglycerides (TG) and total lipid levels in an induced hypercholesterolemic Wistar albino rats.

Twenty male Wistar albino rats were used in this study. They were divided into four groups A, B, C and D. Group A (control group) received a basal diet, group B received a basal diet with 2% cholesterol, group C received a basal diet with 2% cholesterol and 4% sativum fruits powder, group D received a basal diet with 2% cholesterol and 8% sativum fruits powder.

The results showed that, plasma TC, LDL-c, TG and total lipid were increased significantly ($P < 0.05$) in group B compared to the control group, while HDL-c level was decreased significantly compared to the control.

In group C, the plasma levels of TC, LDL-c, TG and total lipid were non-significantly lower compared to group B, while, HDL-c was non-significantly higher compared to group B. The plasma levels of TC, LDL-c, TG and total lipid in group C were significantly ($P < 0.05$) higher compared to group D, while, HDL-c was significantly ($P < 0.05$) lower compared to group D.

The plasma levels of TC, LDL-c, TG and total lipid in group D were decreased significantly ($P < 0.05$) compared to group B, while HDL-c was significantly ($P < 0.05$) increased. The levels of TC, LDL-c, HDL-c, TG and total lipid in group D were non-significantly different compared to the control group.

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INTRODUCTION

Lipids are usually defined as those compounds that are soluble in organic solvents but are insoluble in water. Lipids are one of the major constituents of foods and important in diet because they are the major source of energy and provide essential lipid nutrients. This group of substances includes, triglycerides, diglycerides, monoglycerides, free fatty acids, phospholipids, and cholesterol, but the triglycerides are the major component of most foods, they represent 95 to 99% of the total lipid present. The most important precursor and derived lipids is the cholesterol because it is the best known sterol, and it is a precursor of a large number of important steroids such as: bile acids, sex hormones, adrenocortico-hormones, vitamin D and alkaloids (Murray *et al.*, 1999).

Cholesterol is present mainly in blood in the lipoprotein fractions: low density lipoprotein and high density lipoprotein. Cholesterol value comes from its association with atherosclerosis when cholesterol level increases and deposited in the blood vessels especially the coronary arteries which is the risk factor that may result in heart disease (Kumar *et al.*, 1987).

There are many chemical drugs like: statins, ezetimibe and nicotinic acid that lower cholesterol level but are most expensive and have many undesirable effects (Thomas, 2003). Many herbal plants that lower cholesterol concentration were studied by Prasanna (2000), El-Dakhakhny *et al.* (2000) and Sen and Bhattacharyya (2001).

In Sudan sativum fruits is traditionally used in cooking and against flatulence. The first study of the hypolipidemic action of sativum fruits begins in India which is known as the "spicy country" the Indian scientists gave the sativum fruits powder to Wistar albino rats by oral intubation after mixing the fruits powder with distilled water (D.W) (Chithra and Leelamma, 1997). There is another study found in Korea, where coriander whole fruits were fed to Sprague-Dawley rats after feeding of a high fat diet (Hwang *et al.*, 2001). In Japan, Ertas and Guler (2005) fed the Japanese quails coriander whole fruits after feeding of a high fat diet.

Since there are no scientific studies that investigate the hypolipidemic effect of sativum fruits powder mixed diet. Therefore, the objective of this study is to investigate the effect of feeding sativum fruits powder mixed diet on the level of lipid profile in an induced hypercholesterolemic Wistar albino rats.

CHAPTER ONE

LITERATURE REVIEW

1.1 Lipids:

Lipids are heterogeneous group of biomolecules that are insoluble in water, but are soluble in organic solvents like benzene, ether, and chloroform (Murray *et al.*, 1999). Chemically lipids include compounds that yield fatty acids on hydrolysis and complex alcohol that can combine with fatty acids to form esters (Norbert, 1987).

Lipids are important dietary constituents because of the fat-soluble vitamins and the essential fatty acids contained in the fat of natural foods. Lipids play many roles in biological system, like carbohydrate they are an important source of energy. In addition they can also serve as padding and thermal insulator (Lehninger *et al.*, 1997).

Combination of fat and protein (lipoproteins) are important cellular constituents occurring in the cell membrane and in the mitochondria and serving as the means of transporting lipids (Murray *et al.*, 1999).

1.1.1 Cholesterol:

Cholesterol is the best known steroid; because of its association with atherosclerosis. Cholesterol is the parent molecule from which all steroids in the body are synthesized, which includes bile acids, adrenocortico-hormones, sex hormones, vitamin D, cardiac glycosides, and some alkaloids (Murray *et al.*, 1999).

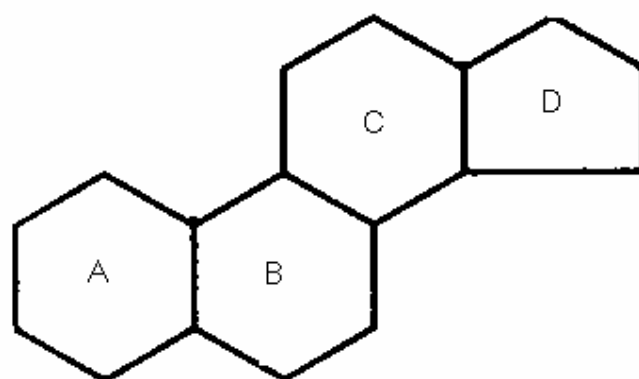
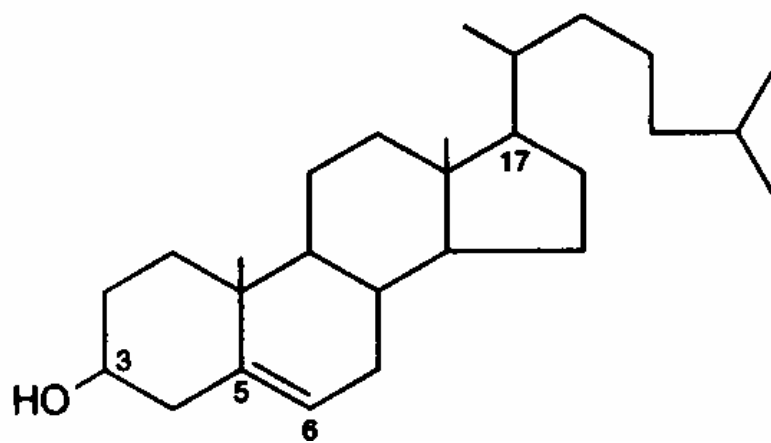
Like other sterols, cholesterol is a solid alcohol of high molecular weight and possesses the tetracyclic perhydrocyclopentane-

phenanthrene skeleton (Norbert, 1987). The molecule contains 27 carbon atoms as shown in Fig. (1).

In plasma cholesterol is found in the esterified form with the fatty acids whereas, in cells it is free. Because cholesterol [like all other lipids] is insoluble in water, it is carried in the blood bound to a protein mixture, forming molecules called "lipoproteins". The two types of lipoproteins that are particularly important in atherosclerosis and coronary heart disease are low density lipoproteins (LDL) and high density lipoproteins (HDL). LDL transports cholesterol from the liver (where cholesterol is synthesized) to peripheral tissues of the body. Whereas, HDL removes excess cholesterol from peripheral tissues, taking it back to the liver to be broken down. The liver plays an important role in the regulation of the body's cholesterol balance (Lalitha, 1996).

1.1.2 Lipoproteins:

Fat absorbed from the diet and lipids synthesized by the liver and adipose tissue must be transported between the various tissues and organs for utilization and storage. Lipoproteins are the main transported form of lipids, these lipoproteins were separated from plasma by using ultracentrifugation technique. There are four major groups of plasma lipoproteins which are important physiologically and clinically. These classes include chylomicrons, which are derived from the intestinal absorption of triglycerides; very low density lipoprotein (VLDL), synthesized in the liver for the export of triglycerides to peripheral tissues; low density lipoprotein (LDL),



perhydro cyclopentano phenanthrene skeleton

Fig. (1): Structure of cholesterol

representing a final stage in the catabolism of VLDL; and high density lipoprotein (HDL) which is involved in VLDL and chylomicrons metabolism and also in cholesterol transport. Triglycerides are the predominant lipids in chylomicrons and VLDL, whereas, cholesterol and phospholipids are the predominant lipids in LDL and HDL respectively (Murray *et al.*, 1999).

Also there is a transient lipoprotein called intermediate lipoprotein, which is usually undetectable in normal plasma. It is formed during the conversion of VLDL to LDL. It contains both cholesterol and endogenous triglycerides (Zilva *et al.*, 1994).

1.1.2.1 Low-density lipoprotein (LDL):

Low density lipoprotein (LDL) is the main cholesterol carrying lipoprotein in the circulation. The protein component is exclusively apo B-100 which is critical for lipid transport (Packard *et al.*, 2003). It has longer life than its precursors VLDL and IDL, and accounts for about 70% of the total cholesterol in plasma.

VLDL takes cholesterol which is synthesized by the liver and transports it to the extra-hepatic tissues. In the circulation VLDL is converted to LDL through the action of lipoprotein lipase (Michael, 2006). LDL taken up by cells via LDL receptor mediated endocytosis (apo B/E receptors). The uptake of LDL occurs predominantly in the liver (75%), adrenals and adipose tissue (Packard *et al.*, 2003). After entering cells LDL particles are broken down by lysosomes, much of the released cholesterol contributes to membrane formation or in the adrenal cortex and gonads to steroid synthesis. Excess intracellular cholesterol is re-esterified by acylCoA cholesterol acyl transferase

(ACAT) for intracellular storage. The activity of ACAT is enhanced by the presence of intracellular cholesterol (Murray *et al.*, 1999).

Increasing amount of cholesterol reaching the liver from the intestine will reduce LDL receptors number, and so lead to accumulation of cholesterol in the liver, this will prevent LDL entry into cells, therefore, their plasma concentration rises (Zilva *et al.*, 1994), so enhanced the deposition of cholesterol in the blood arteries especially coronary arteries leading to atherosclerosis (Kumar *et al.*, 1987).

1.1.2.2 High density lipoprotein (HDL):

High density lipoprotein (HDL) forms a class of lipoprotein, which carries cholesterol from the body's tissue to the liver. Because HDL can remove cholesterol from atheroma within arteries, and transport it back to the liver for excretion or reutilization, they are called as “good” lipoproteins.

HDL is the smallest of the lipoproteins. It is the densest because it contains the highest proportion of proteins (Zilva *et al.*, 1994). It contains the A class of apolipoproteins (nascent discoidal HDL), apo C and E are synthesized in the liver and transferred from the liver HDL to intestinal HDL. A plasma enzyme called lecithin-cholesterol acyl transferase (LCAT) converts the free cholesterol into cholesteryl ester which is then sequestered into the core of the lipoprotein particle eventually making the newly synthesized HDL spherical (HDL₃). It becomes less dense forming HDL₂ which delivers the cholesterol to the liver. Hepatic lipase hydrolyzes HDL phospholipids and triglycerides allowing the particle to release cholesteryl ester to the

liver, then the particle become more dense, reforming HDL₃, which reenters the cycle (Murray *et al.*, 1999, Peter, 2004).

1.1.3 Triglycerides:

The triglycerides are esters of alcohol glycerol and fatty acids. They are the main storage form of fatty acids, they represent the most important class of dietary fats which constitute more than 90% of the dietary lipids (Sheriff, 2004). These compounds also supply the body with the essential fatty acids required, in addition to energy (Champe and Harvey, 1994; Murray *et al.*, 1999). When there is an excess in body's calories, the liver synthesizes the triglycerides, then transported and stored in the adipose tissue. A recent study showed that having high levels of triglycerides, increase the risk of having heart attack (Mirkin, 2000). Indeed many people with high levels of plasma triglycerides were found to have low levels of HDL (Kelly, 2002).

1.1.4 Total lipid:

The term "total lipid" refers to all lipids content in the tissues and blood. The lipids are extracted by a solvent system based usually on a mixture of chloroform and methanol (Waite, 1996). Christie (1982) extracted about 13 bands of lipids, cholesterol, triglycerides and cholesterol ester are the major components, and monoacyl glycerols and phospholipids are the minor. Bruce (1996) isolated free fatty acids and phospholipids. Triglycerides are the more efficient storage form of energy (Trudy and James, 1996).

The phospholipids are amphipathic molecules, which are the structural component of membranes. Phospholipids have two types:

first, glycerophospholipids which contain glycerol as a backbone, and include phosphatidic acid which considered as the parent of the phospholipids, and lecithins which are the major glycerophospholipids (Abraham and Benjamin, 1971).

The second type includes sphingolipids, which contain sphingosine as a backbone, for example sphingomyelin which is the important component of animal and plant membrane (Evans and Dodd, 1990).

The other important total lipids constituents are the fatty acids, which occur as free or esterified. The esterified fatty acids stored as a fuel molecules known as triglycerides. The free fatty acids can combine with albumin for transport to target tissues. In the biological system fatty acids contain an even number of carbon atoms, typically between 14 and 24, the 16 and 18 carbon fatty acids are most common. These fatty acids may be saturated which have no double bonds or may be unsaturated which contain one or more double bonds (Russel, 1989).

The fatty acids have three major physiological roles. First, they are building blocks of phospholipids and glycolipids. Second, fatty acids derivatives serve as hormones and intracellular messenger. Third, fatty acids are fuel molecules, they are stored as triglycerides (Lubert, 1988).

1.2 Hypolipidemic agents:

1.2.1 Drugs:

Cholesterol reducing drugs are medications that lower the levels of fats in the blood, including cholesterol, LDL-cholesterol (LDL-c)

and triglycerides. High levels of these fats in the blood stream increase the risk of atherosclerosis, heart attack, stroke and other heart related conditions. Therefore, cholesterol reducers and other antilipidemic medications are often prescribed for people with high cholesterol levels (hypercholesterolemia) or other elevated lipid level (e.g. high triglycerides) (Ozkan *et al.*, 2004).

These chemical drugs such as bile resins acids, statins, ezetimibe, colestide, cholestyramine and nicotinic acid have severe side effects, like interfering with the absorption of other substances including other medication, or flushing as seen in nicotinic acid at large doses (Thomas, 2003).

These facts prompted the scientists world wide to embark on research on medicinal plants as they are a potential source of many substances of clinical interest (Ozkan *et al.*, 2004).

1.2.2 Plants:

1.2.2.1 Soybean genistein:

Administration of genistein to rats at a dose of 5 to 8mg/day/100g body weight (Bwt) for 12 days inhibited the incorporation of acetate into cholesterol and fatty acids in liver. The genistein enhances bile formation and biliary lipid secretion, also the activity of hydroxy-methyl-glutaryl-CoA reductase (HMG-CoA reductase) and cholesterol hydroxylase was decreased, and the microsomal acyl-CoA cholesterol acyl transferase (ACAT) showed a dramatic decrease (Kojima *et al.*, 2002).

1.2.2.2 Mangiferin:

Feeding mangiferin roots at a dose rate of 20% mixed with mice diet for 14 days, increases bile acid excretion and reduced blood cholesterol levels in hypercholesterolemic mice, this is due to the fiber content of the plant (Miura *et al.*, 2001).

1.2.2.3 Sunflower seeds:

Phytosterol which is similar to the structure of cholesterol extracted from the sunflower seeds showed a significant decrease in plasma cholesterol and triglycerides concentration when present in a sufficient amount, this is due to the high fecal excretion of bile acids (Sen and Bhattacharyya, 2001).

1.2.2.4 Jasmine green tea:

Epicatechins, which is isolated from jasmine green tea showed a hypolipidemic effect when added at a dose of 200g mixed with 1 g of cholesterol to hamsters diet for 4 weeks. The hamsters had higher fecal excretion of fatty acids, neutral and acidic sterols. This study suggested that the hypolipidemic activity of jasmine green tea is not due to the inhibition of cholesterol and fatty acid synthesis but is most likely mediated by its influence on excretion of dietary fat and cholesterol (Chan *et al.*, 1999).

1.2.2.5 Ginger (Zingiber officinale R.):

Oral administration of ginger at a dose of 35 and 70 mg/kg Bwt to rats by intragastric intubation daily for 10 weeks decreased significantly the levels of cholesterol, phospholipids and free fatty acids in the tissues (liver, kidney, intestine, and aorta) and serum. Levels of serum triglycerides were also significantly reduced.

Supplementation of ginger increased the concentration of HDL-cholesterol (HDL-c) and decreased the concentration of LDL-c and VLDL in the serum. Dietary intake of ginger was found to reduce the risk of atherosclerosis (Murugaiah *et al.*, 1999).

1.2.2.6 Fenugreek (Trigonella foenum-graecum):

Administration of powdered and extracted fenugreek seeds to human patients at a dose of 25 and 50 g given orally before lunch and dinner every day for 20 days reduced serum cholesterol and triglycerides as well as VLDL. The saponine present in the plant fiber enhanced the fecal excretion of bile acids which increases the conversion of cholesterol into bile acids (Prasanna, 2000).

1.2.2.7 Nigella sativa:

Nigella sativa seeds when fed to broiler chicks at a dose of 0.75% resulted in a significant reduction in serum total lipids concentrations (Abdel-Mageed, 1999). Also *sativa* was shown to reduce serum cholesterol in human when was used for two weeks at a dose of 2 mg/day (Bamosa *et al.*, 1997). In addition, *sativa* oil was reported to reduce serum total cholesterol and triglycerides when was given orally to rats at a dose of 800 mg/kg Bwt. for 4 weeks. This is may be due to thymoquinone which is an important component of the seeds which increases the conversion of cholesterol into bile acids (EL-Dakhakhny *et al.*, 2000).

1.2.2.8 Hawthorn fruit (Crateagus spp):

Two grams of hawthorn fruits powder added to a high cholesterol diet, fed to rabbits for 12 weeks decreased serum total cholesterol, LDL-c and triglycerides levels. The mechanism by which

hawthorn fruit decreases serum cholesterol is due to the inhibition of cholesterol absorption mediated by down regulation of intestinal Acyl-CoA cholesterol-acyl-transferase (ACAT), also hawthorn fruit had a good fecal excretion of acidic and neutral sterols. Supplementation of hawthorn fruit did not affect the activities of hepatic 3-hydroxy-3-methyl glutaryl CoA reductase (HMG-CoA reductase) or cholesterol hydroxylase (Anthony and Walter, 2000).

1.2.2.9 Guar gum:

Guar gum at dose rate of 30% reduced total cholesterol and triglycerides in plasma and liver of diabetic and non-diabetic rats when fed for 2 weeks. The mechanism is due to the high amount of fibers that bind to bile acids and excreted them out of the body (Yamamoto, 2001).

1.2.2.10 Gum Arabic:

Gum Arabic showed a significant lipids lowering effect in rats when fermented. This is due to the arabin which contains omega 3 fatty acids which are responsible for the blockage of lipids synthesis (Moundras *et al.*, 1994).

1.2.3 Fibers:

Soluble fibers have greater potential to alter serum lipid concentration (Glore *et al.*, 1994). High fiber intake was found to be associated with lower serum cholesterol concentration (Anderson *et al.*, 1994). Also pectin was shown to reduce cholesterol and triglycerides (Vigne, 1987; Park *et al.*, 2000).

1.3 General taxonomy of *Coriandrum sativum*:

Vernacular name: (Ar) Kuzbara

Family: Coriander – Umbelliferae (Bown, 1995).

Botanical description:

It is an annual herb of the carrot family. Umbelliferae- up to 60 cm. Erect, glabrous stems with a strong scent. Compound leaves, bipinnate or tripinnate; the lower ones with longer stems and with narrow segments than superior ones. Whitish flowers in umbels, with till 8 rays. The fruits have a brown yellow colour as seen in Fig.3 with very scented odour (Diederichsen, 1996).

Scientific classification:

Kingdom: Plantae
Division : Magnoliophyta
Class : Magnoliposida
Order : Apiales
Family : Apiaceae
Genus : *Coriandrum*
Species : *C. sativum*

Habitat:

Native from Asia and Africa, it can be found as a cultivated plant (Wichtl and Bisset, 1994).

Folkloric use:

Coriandrum sativum fruits powder is used against flatulence and as an antibacterial. Also in India it is used against hyperlipidemia (Leung and Foster, 1996).

1.3.1 Chemical composition of *Coriandrum sativum*:

Many chemical substances were isolated from *sativum* by aqueous and alcoholic extraction. The aqueous extraction obtained some acids like, linoleic, oleic, palmitic acid, α -linolenic acid which is

the important omega 3 fatty acids, as well as stearic and ascorbic acids (Deng *et al.*, 2003). The alcoholic extraction by steam distillation of coriander seeds, extracted many essential oils, in all samples in which linalool is the main component with a maximum concentration of 81% of the total volatile fractions, coriandrol oil 8% is the second active ingredient of the plant (Tanigwichi *et al.*, 1996). Also there are minor volatile oils like, camphor 5.6%, geraniol 1.5%, geranyl acetate 4% as well as cineole, Borneol, Citronelol, limonene, alpha pinene, beta pinene and beta phelandrene (Boselah, 1995). Also some minerals in the leaves and seeds of the *sativum* plant were discovered like, calcium, manganese, potassium, magnesium, phosphorus and sodium (Chevallier, 1996), the plant contains also high amount of fibers (Sairam, 1998).

1.3.2 Health benefits of *Coriandrum sativum*:

sativum seeds have a health supporting reputation that is high on the list of the healing spices (Leung and Foster, 1996). In parts of Europe, coriander has traditionally been referred to as an "antidiabetic plant" (Gray and Flatt, 1999). The volatile oils found in the leaves of this plant may have antimicrobial properties. In parts of India it has traditionally been used for its anti-inflammatory properties, because it heals the digestive mucous membrane (Simone *et al.*, 1984).

sativum relieves colds, combats diarrhea and intestinal poisoning, also it is used for toothache and mouth wash (Anon, 1999). The plant has anti-convulsant effect (Hussein, 1999). Coriander seeds oil is an aromatic stimulant, carminative, an appetizer and a digestive stimulant for the stomach and intestine (Simone *et al.*, 1984). It has hypotensive effect (Medhin *et al.*, 1986).

Coriander cakes were once taken against "St-Anthony's fire" or "Rose" a severe streptococcal skin infection (Wichtl and Bisset, 1994). In Asia the herb is used against headache, swelling and used as a paste for mouth ulceration and poultice for other ulcers (Simone *et al.*, 1984; Anon, 1999).



Fig. (2) *sativum* plant



Fig. (3) *sativum* fruits

CHAPTER TWO

MATERIALS AND METHODS

2.1 Experimental details:

This experiment was designed to investigate the effect of feeding *sativum* fruits powder supplemented diet on plasma lipid levels in an induced hypercholesterolemic Wistar albino rats (*Rattus norvegicus*).

2.1.1 Experimental animals:

Twenty Wistar albino male rats obtained from the University of Khartoum, Faculty of Veterinary Medicine were used in this study. The rats were housed identically in stainless steel cages in an air room under a 12-h light: dark cycle. All of the rats were initially fed a standard laboratory diet for at least 7 days to acclimatize to our laboratory. Tap water was freely available. They were divided into four groups of five rats each.

2.1.2 The rat basal diet:

The rats were given a basal diet which fulfilled their requirement. The diet composition was as follows:-

Wheat flour	692 g
Dry meat	165 g
Sodium chloride	3 g
Oil	120 g

2.2 Plant material:

sativum dry fruits brought from the local market were purified and powdered then added to the diet.

2.3 cholesterol supplementation in the rat diet:

2% cholesterol powder was supplemented to the basal diet of the rats so as to induce hypercholesterolemia in all groups except the control, according to Chithra and Leelamma (1997).

2.4 Equipment used:

- Heparinized capillary tubes.
- Heparinized blood containers.
- Plane containers.
- Centrifuge (Gallenkamp).
- Automatic pipettes.
- Roche diagnostic/Hitachi 902 analyzer.

2.4.1 Chemicals:

Cholesterol powder (the British Drug House Ltd).

2.5 Experimental procedure:

The animals were divided into four groups of five animals each. These groups were named as A, B, C, and D. Group A was given the basal diet and served as control, group B received 2% cholesterol added to the basal diet. Group C received 2% cholesterol and 4% *sativum* fruits powder added to the basal diet, while group D received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet. Blood samples were collected after two weeks following treatment so as to confirm the induction of hypercholesterolemia. Then after another two weeks the blood samples were taken for the determination of different lipid fractions.

2.5.1 Blood sampling:

1.5 ml of blood was collected from the rat's orbital plexus after an overnight fast by capillary tubes and was put in heparinized containers, the blood was centrifuged at 5000 rpm for 10 min. then the plasma was placed into plane containers and stored at -20°C until analysis.

2.6 Analytical Methods:

2.6.1 The Roche diagnostics/Hitachi 902 analyzer:

All different lipid fractions were measured by using the Roche diagnostics Hitachi 902 Analyzer. It is an analyzer used to report test results on various body fluids samples for wide range of analyses as seen in Fig. (4). It is fully automated, computerized, performs potentiometric and photometric assays, and includes analytical processing unit and luminance crystal display (LCD) touch screen, with a standard printer to print out the results. The analyzer is characterized by doing two hundred photometric tests per hour, and refrigerated storage for forty reagents containers, as well as it has end point, kinetic and isoenzymes reactions.

2.6.2 Determination of plasma total cholesterol:

Principle:

Total cholesterol in the sample originates by means of the coupled reactions described below. By the action of cholesterol esterase the free cholesterol is released from the cholesteryl ester. Then cholesterol reacts with oxygen by cholesterol oxidase to form hydrogen peroxide, then hydrogen peroxidase releases the quinoneimine pigment from 4-aminoantipyrine.

Cholesteryl ester + H₂O $\xrightarrow{\text{Cholesterol esterase}}$ cholesterol + fatty acid

Cholesterol + 1/2O₂+H₂O $\xrightarrow{\text{cholesterol oxidase}}$ Cholestenone + H₂O₂

H₂O₂ + Phenol+ 4 –aminoantipyrine $\xrightarrow{\text{Peroxidase}}$ quinoneimine (pink) + H₂O

Reagents:

- Good's buffer PH 6.7 50 mmol/L.
- Phenol 28mmol/ L.
- 4-aminoantipyrine 0.9 mmol/L.
- Cholesterol esterase 4000 U/ml.
- Cholesterol oxidase 20000 U/ml.
- Peroxidase 20000 U/ml.
- Sodium cholate 28 mmol/L.

2.6.3 Determination of plasma low density lipoprotein cholesterol

(LDL-c):

Principle:

In this method LDL-c is selectively protected from lipoprotein lipase by protecting reagent (R₁), then in the second step LDL-c is released and selectively determined by releasing reagent (R₂).

Cholesterol ester+H₂O $\xrightarrow{\text{Cholesterol esterase}}$ Cholesterol+ fatty acid

Cholesterol +1/2O₂+H₂O $\xrightarrow{\text{Cholesterol oxidase}}$ Cholestenone + H₂O₂

2H₂O₂ $\xrightarrow{\text{Catalase}}$ 2H₂O+O₂

H₂O₂ + Phenol + 4-aminoantipyrine $\xrightarrow{\text{Peroxidase}}$ Quinoneimine (blue colour complex) + 2H₂O

Reagents:

Reagent (1) consists of:

- | | |
|------------------------|------------|
| - Good's buffer PH 6.8 | 30 mmol/L |
| - Cholesterol esterase | 4000 IU/L |
| - Cholesterol oxidase | 20000 IU/L |
| - Catalase | 4000 IU/L |

Reagent (2) consists of:

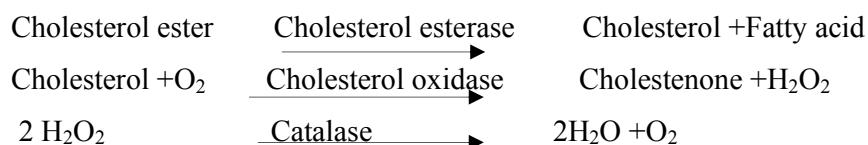
- | | |
|------------------------|------------|
| - Good's buffer PH 7.0 | 30 mmol/L |
| - Peroxidase | 2400 IU/L |
| - 4-aminoantipyrine | 0.9 mmol/L |
| - Sodium azide | 0.9 mmol/L |

2.6.4 Determination of plasma high density lipoprotein-cholesterol (HDL-c):

Principle:

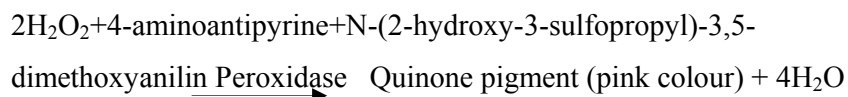
It is a direct method consisting of two steps:

1. Elimination of chylomicron, VLDL, LDL by cholesterol esterase, cholesterol oxidase and subsequently cholesterol Catalase.



2. Specific measurement of the release of HDL-c:-

After the release of HDL-c by detergent in reagent (2), the intensity of quinoneimine dye produced is directly proportional to the cholesterol concentration when measured at 600 nm.



Reagents:

Reagent (1) consists of:

- Good's buffer PH 6.6 30 mmol/L
- Ascorbate oxidase 2700 IU/L.
- Catalase 4000 IU/L.
- Cholesterol oxidase 20000 IU
- Cholesterol esterase 4000 IU/L.
- Surfactants

Reagent (2) consists of:

- Good's buffer PH 7.0 30 mmol/L.
- 4-aminoantipyrine 0.9 mmol/L.
- Peroxidase 2400 IU/L.
- Sodium azide 0.9 mmol/L.



Fig. (4): Hitachi 902 automatic analyzer

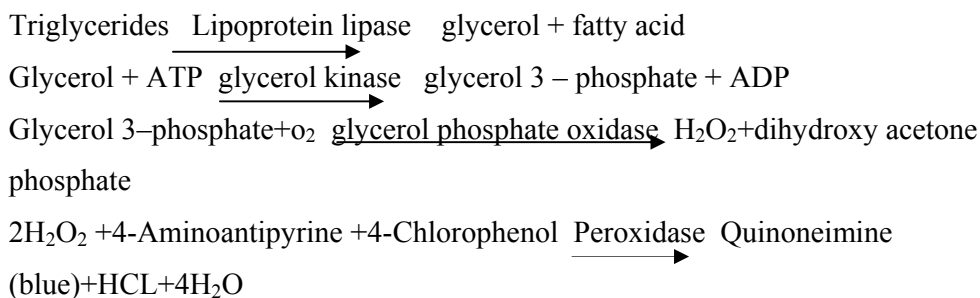


Fig. (5): Hitachi sample cups

2.6.5 Determination of plasma triglycerides:

Principle:

They were determined after enzymatic splitting with lipoprotein lipase. The indicator is quinoneimine which is generated from 4-aminoantipyrine and 4-chlorophenol by hydrogen peroxide under the catalytic action of Peroxidase.



Reagents:

-Good's buffer PH 7.2	50mmol/L.
-4-chlorophenol	4 mmol/L.
-Magnesium chloride	15 mmol/L.
- ATP	2 mmol/L.
-Peroxidase	0.8 IU/L.
- Glycerol kinase	1.5 IU/L.
-Lipoprotein lipase	100 IU/ml.
- Glycerol-3-phosphate oxidase	4 IU/L.
- 4-Aminoantipyrine	0.9 mmol.

2.6.6 The analyzer procedure:

For the determination of each parameter, 0.5 ml of plasma was put in Hitachi sample cups (Fig. 5). The sample cups were entered in a specific place on the analyzer and then the parameters to be measured were selected and registered in the screen. Thereafter, the machine was put on and the results were printed in ten minutes.

2.6.7 Determination of plasma total lipids:

Principle:

Total lipids were determined by phosphovanillin reaction according to Frings *et al.* (1972). Lipids react with vanillin in a medium of sulphuric and phosphoric acids to form a chromogen, and the absorbance is measured with a colorimeter.

Reagents:

- Concentrated sulphuric acid.
- 0.6% vanillin reagent [it is made by mixing 6.0 g of vanillin with a Liter of distilled water (D.W)].
- Phospho-vanillin reagent (200 ml) (it is made by mixing 6.0 g of vanillin with 800 ml concentrated Phosphoric acid)

Procedure:

0.1 ml of the sample was added to 2.0 ml of concentrated sulphuric acid. Then the mixture was mixed and put in a boiling water bath for 10 min. so as to be digested. Thereafter, 1 ml of the digest was added to 5 ml phosphovanillin reagent. The mixture was mixed well and incubated at 37°C for 15 min., then the optical density (O.D) was read at 540 nm using a colorimeter.

Calculations:

$$\text{Total lipids (mg/dl)} = \frac{\text{O.D of the sample}}{\text{O.D of the standard}} \times \text{concentration of the standard}$$

2.7 Statistical analysis:-

Two groups compared test (T-test) was used for the statistical analysis of data (Gomez and Gomez, 1984) with the aid of statistical package for social science programme (SPSS).

CHAPTER THREE

RESULTS

3.1 The induction of hypercholesterolemia:

The results of induction of hypercholesterolemia are shown in Table (1) and Fig. (6). There is a significant increase in the total cholesterol level as well as LDL-c, but a significant decrease in the HDL-c level in group B compared to the control group.

Table (1): The levels of total cholesterol, and its fraction low density lipoprotein, and high density lipoprotein in group B compared to group A two weeks after the induction of hypercholesterolemia

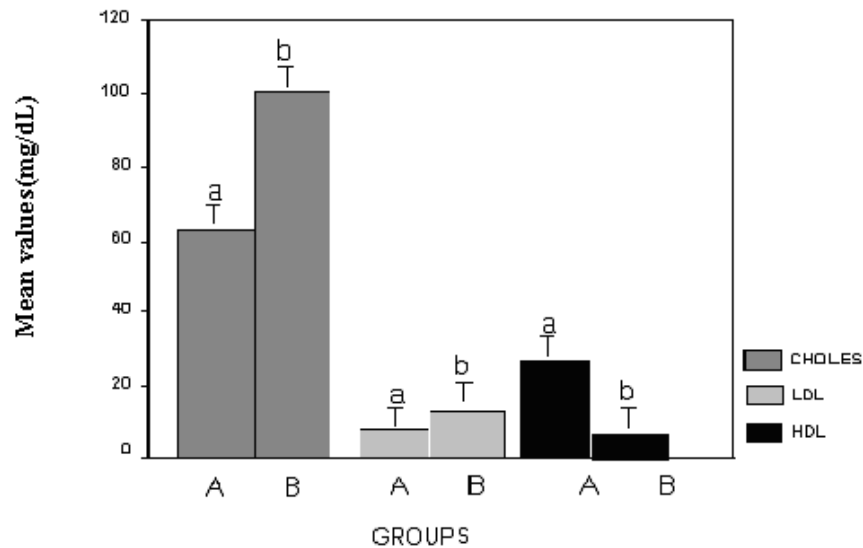
Parameters Groups	Total cholesterol	Low density lipoprotein cholesterol	High density lipoprotein cholesterol
A	62.7±23.25 ^a	8.03±1.08 ^a	26.87±11.48 ^a
B	100.6±15.15 ^b	13.04±5.75 ^b	7.53±3.95 ^b

Means ± (SE) within the same column having different small superscript letters are significantly different at (P < 0.05) based on T-test

Group A: Received the basal diet and served as control.

Group B: Received 2% cholesterol added to the basal diet.

Fig. (6): The levels of total cholesterol, and its fractions low density lipoprotein, and high density lipoprotein in group B compared to group A two weeks after the induction of hypercholesterolemia



Bars having different small superscript letters are significantly different at ($P < 0.05$) based on t-Test.

Group A: Received the basal diet.

Group B: Received 2% cholesterol added to the basal diet.

3.2 The effect of feeding *sativum* fruits powder on the plasma total cholesterol level in an induced hypercholesterolemic Wistar albino rats:

The results of plasma total cholesterol levels of group A, B, C and D are presented in Table (2) and Fig. (7). The level of plasma total cholesterol in group B is significantly ($P < 0.05$) higher than the control (group A). In group C the level of plasma total cholesterol is non-significantly lower than group B, while it is significantly ($P < 0.05$) higher compared to group D and the control. However, in group D the level of plasma total cholesterol is significantly ($P < 0.05$) lower compared to group B and non-significantly different from the control.

3.3 The effect of feeding *sativum* fruits powder on the plasma low density lipoprotein levels in an induced hypercholesterolemic Wistar albino rats:

The results of plasma LDL-c levels of group A, B, C and D are presented in Table (2) and Fig. (8). The level of plasma LDL-c in group B is significantly ($P < 0.05$) higher when compared to group A. In group C The level of plasma LDL-c is non-significantly lower than group B, while it is significantly ($P < 0.05$) higher compared to group D and the control. However, in group D the level of plasma LDL-c is significantly ($P < 0.05$) lower than group B and non-significantly different from the control.

Table (2): The effect of feeding *sativum* fruits powder on the levels of total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, and total lipids in an induced hypercholesterolemic Wistar albino rats.

Parameters Groups	Total cholesterol (mg/dl)	Low density lipoprotein (mg/dl)	High density Lipoprotein (mg/dl)	Triglycerides (mg/dl)	Total lipids (mg/dl)
A	61±5.37 ^a	13.42±1.2 ^a	25.52±2.15 ^a	90±6.72 ^a	220±13.38 ^a
B	154.2±3.56 ^b	130.36±9.12 ^b	9.41±2.27 ^b	220±13.36 ^b	533.4±36.52 ^b
C	140.2±11.19 ^b	102.7±7.18 ^b	13.55±3.27 ^b	125±7.59 ^b	467±10.77 ^b
D	117±6.09 ^a	23.61±2.11 ^a	20.97±2.14 ^a	82±3.97 ^a	231.2±12.97 ^a

Means ± (SE) within the same column followed by different superscript small letters are significantly different at (P<0.05) based on t-Test.

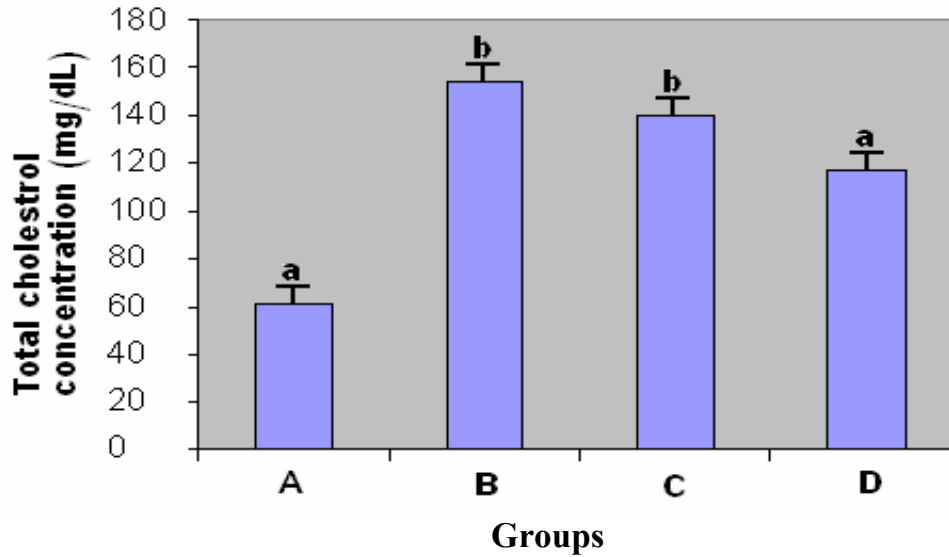
Group A: Received the basal diet.

Group B: Received 2% cholesterol added to the basal diet.

Group C: Received 2% cholesterol and 4% *sativum* fruits powder added to the basal diet.

Group D: Received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet.

Fig. (7): The effect of feeding *sativum* fruits powder on the plasma total cholesterol level in an induced hypercholesterolemic Wistar albino rats:



Bars having different small letters are significantly different at ($P < 0.05$) based on t-Test.

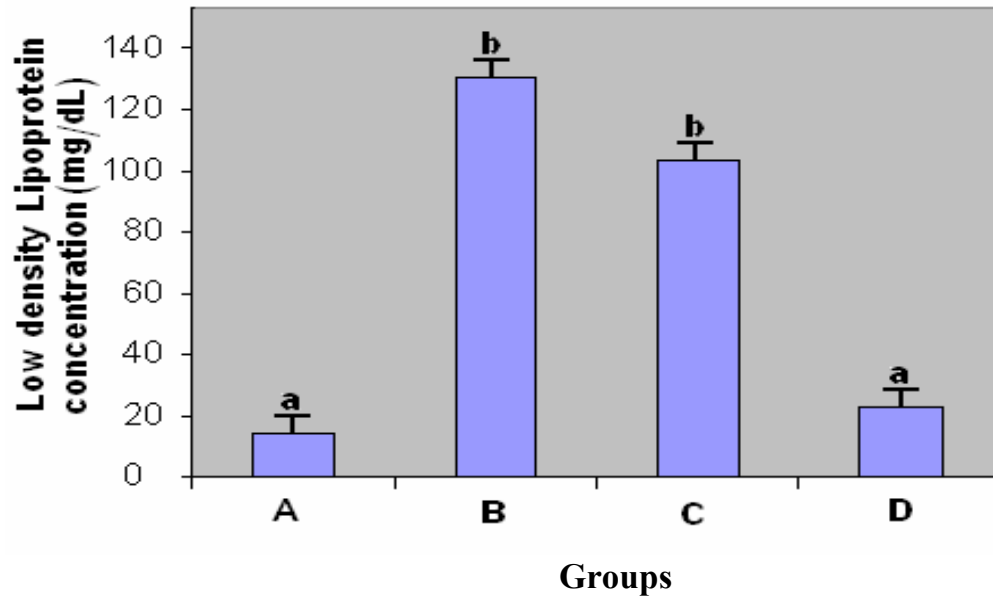
Group A: Received the basal diet.

Group B: Received 2% cholesterol added to the basal diet.

Group C: Received 2% cholesterol and 4% *sativum* fruits powder added to the basal diet.

Group D: Received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet.

Fig. (8): The effect of feeding *sativum* fruits powder on the plasma LDL-c level in an induced hypercholesterolemic Wistar albino rats:



Bars having different small letters are significantly different at ($P < 0.05$) based on t-Test.

Group A: Received the basal diet.

Group B: Received 2% cholesterol added to the basal diet.

Group C: Received 2% cholesterol and 4% *sativum* fruits powder added to the basal diet.

Group D: Received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet.

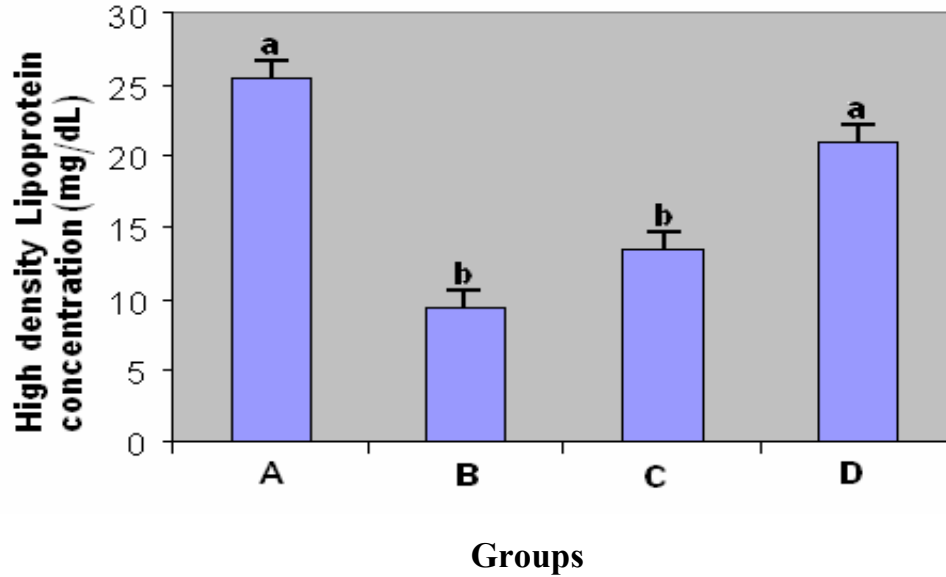
3.4 The effect of feeding *sativum* fruits powder on the plasma HDL-c levels in an induced hypercholesterolemic Wistar albino rats:

The results of plasma HDL-c levels of group A, B, C and D are presented in Table (2) and Fig. (9). There is a significant decrease ($P < 0.05$) in HDL-c level in group B when compared to the control (group A). In group C the level of plasma HDL-c is non-significantly (higher compared to group B, while it is significantly ($P < 0.05$) lower compared to the control. In group D the level of plasma HDL-c is significantly ($P < 0.05$) higher compared to group B and C, while it is non-significantly different from the control.

3.5 The effect of feeding *sativum* fruits powder on the plasma triglycerides level in an induced hypercholesterolemic Wistar albino rats:

The results of plasma triglycerides level of group A, B, C and D are shown in Table (2) and Fig. (10). The level of plasma triglycerides in group B is significantly ($P < 0.05$) higher compared to the control (group A). In group C the level of plasma triglycerides is non-significantly lower compared to group B, while it is significantly ($P < 0.05$) higher compared to the control. In group D the level of plasma triglycerides is significantly ($P < 0.05$) lower when compared to group B and C, and non-significantly different from the control.

Fig. (9): The effect of feeding *sativum* fruits powder on the plasma HDL-c levels in an induced hypercholesterolemic Wistar albino rats:



Bars having different small letters are significantly different at ($P < 0.05$) based on t-Test.

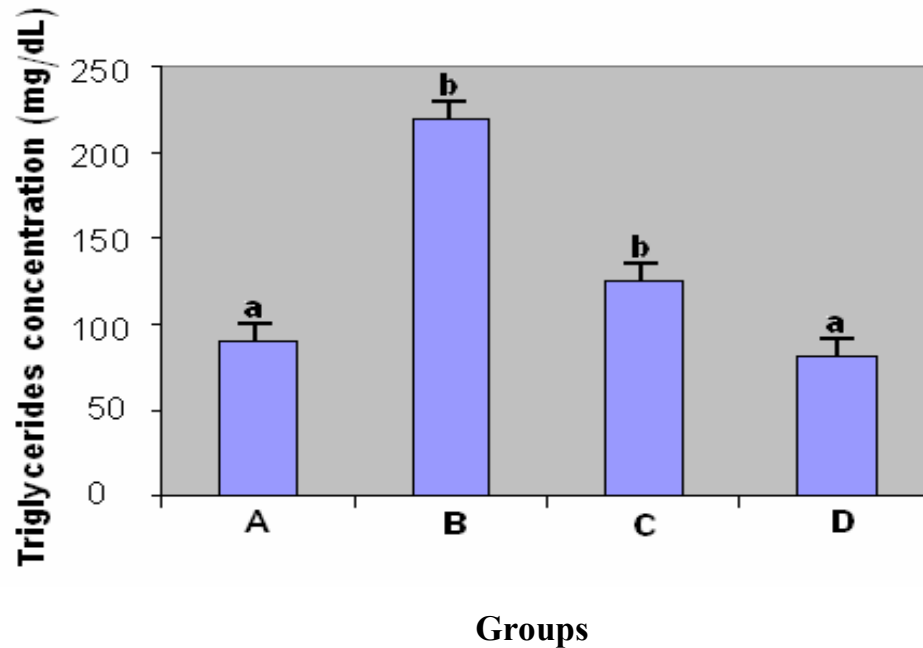
Group A: Received the basal diet.

Group B: Received 2% cholesterol added to the basal diet.

Group C: Received 2% cholesterol and 4% *sativum* fruits powder added to the basal diet.

Group D: Received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet.

Fig. (10): The effect of feeding *sativum* fruits powder on the plasma triglycerides level in an induced hypercholesterolemic Wistar albino rats:



Bars having different small letters are significantly different at ($P < 0.05$) based on t-Test.

Group A: Received the basal diet.

Group B: Received 2% cholesterol added to the basal diet.

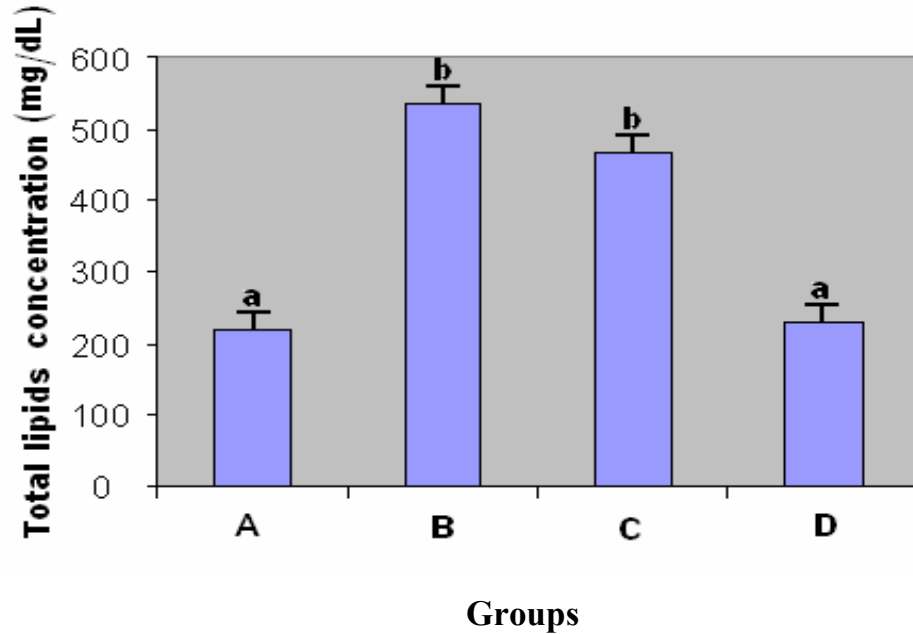
Group C: Received 2% cholesterol and 4% *sativum* fruits powder added to the basal diet.

Group D: Received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet.

3.6 The effect of feeding *sativum* fruits powder on the plasma total lipid levels in an induced hypercholesterolemic Wistar albino rats:

The results of plasma total lipid levels of group A, B, C and D are presented in Table (2) and Fig. (11). The level of plasma total lipid in group B is significantly ($P < 0.05$) higher than the control. In group C the level of plasma total lipid is non-significantly lower compared to group B, while it is significantly ($P < 0.05$) higher compared to group D and the control. However, in group D the level of plasma total lipid is significantly ($P < 0.05$) lower than group B and non-significantly different from the control.

Fig. (11): The effect of feeding *sativum* fruits powder on the plasma total lipid levels in an induced hypercholesterolemic Wistar albino rats:



Bars having different small letters are significantly different at ($P < 0.05$) based on t-Test.

Group A: Received the basal diet.

Group B: Received 2% cholesterol added to the basal diet.

Group C: Received 2% cholesterol and 4% *sativum* fruits powder added to the basal diet.

Group D: Received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet.

Group D: Received 2% cholesterol and 8% *sativum* fruits powder added to the basal diet.

CHAPTER FOUR

DISSCUSSION

sativum plant in a form of oil, powder are widely used for many medications alerts, including healing injuries, lowering blood glucose and reducing lipid profile (Anon, 1999; Budavari, 1996; Chithra and Leelamma, 1997 and Hwang *et al.*, 2001).

Therefore, this study was designed to investigate the effect of *sativum* fruits powder on the plasma level of total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides and total lipids in an induced hypercholesterolemic Wistar albino rats.

4.1 Induction of hypercholesterolemia:

The results showed that plasma total cholesterol and LDL-c were increased significantly ($P < 0.05$) following administration of 2% cholesterol powder added to the basal diet after two weeks in group B compared to the control (group A), but there is a significant ($P < 0.05$) decrease in HDL-c level. These results were in line with the reports from other studies that the administration of cholesterol powder or other high fat diets increase total cholesterol as well as LDL-c, but decrease HDL-c levels (Chithra and Leelamma, 1997; Hwang *et al.*, 2001).

4.2 The effect of feeding *sativum* fruits powder on the level of:

4.2.1 Plasma total cholesterol:

These results showed that the plasma total cholesterol level decreased significantly ($P < 0.05$) following administration of 8% *sativum* fruits powder, which is in line with Chithra and Leelamma

(1997) who reported that feeding of 10% *sativum* fruits powder by ingastric intubation to rats for 75 days resulted in a significant reduction in the serum total cholesterol level and this is may be due to the high fiber amount that increases degradation of cholesterol to fecal bile acids. Also these results agree with Hwang *et al.* (2001), who reported that feeding of *sativum* whole fruits for 5 weeks to rats fed high fat diet is effective in decreasing total cholesterol, which may be attributed to the high fibers content that increases the activity of plasma lecithin cholesterol acyl transferase (LCAT), enhances hepatic bile acids synthesis and increases degradation of cholesterol to fecal bile acids and neutral sterols. Garcia *et al.* (2000) concluded that addition of soluble fibers to atherosclerotic patients increase cholesterol degradation to fecal bile acids. According to Sairam (1998) the coriander seeds contain high amount of fibers and this may be one of an important reasons of the hypocholesterolemic effects of the fruits powder.

On the other hand these results showed that feeding of 4% *sativum* fruits powder did not reduce the level of total cholesterol which may be due to the low fiber content in this percentage or due to the short period of this study. However, these results are in contrast to those of Ertas and Guler (2005), who stated that feeding of 4% coriander seeds to quails for 5 weeks resulted in a significant decrease in total cholesterol level.

According to the above mentioned results the hypocholesterolemic effect of *sativum* fruits powder may be due to the increased activity of plasma lecithin cholesterol acyl transferase (LCAT), enhanced hepatic bile acids synthesis and increased degradation of cholesterol to fecal bile acids and neutral sterols.

4.2.2 Plasma low density lipoprotein:

In the present study 8% *sativum* fruits powder supplementation showed a significant ($P < 0.05$) reduction in plasma LDL-c levels. These results agree with Chithra and Leelamma (1997) who concluded that supplementation of 10% *sativum* fruits powder by oral intubation to hypercholesterolemic rats decreased serum total cholesterol and LDL- c levels and this is may be due to the reduced production and release of LDL-c by liver as well as increased LDL-c receptors activity. Also these results are in line with Hwang *et al.* (2001) who reported that administration of 5 % *sativum* whole fruits to rats after high fat diet reduced LDL-c significantly due to the fiber content that increases LDL-c receptor activity. Diederchsen (1996) reported that coriander fruits contain 16.6 % omega 3 fatty acids and 38.4 % soluble fibers which may play a role in decreasing LDL-c level. Robert (2005) concluded that mixing of 5 and 10 % omega 3 fatty acids with atherosclerotic patients diet reduced LDL-c significantly, this is because omega 3 fatty acids incorporated into atherosclerotic plaques and rupture it. Tsang (2004) suggested that feeding of 5% flax seeds to rats fed high fat diet increased LDL-c receptors which is due to the high amount of omega 3 fatty acids that enhance LDL-c entry into cells.

Feeding 4 % *sativum* fruits powder in this study resulted in a non-significant decrease in LDL-c level which is in contrast to Ertas and Guler (2005). This is may be due the low content of fibers and omega 3 fatty acids in this preparation.

From the above mentioned results reduction in LDL-c levels seen in this study may be due to the reduced production and release of

LDL-c by the liver and an increased LDL-c receptor activity which enhances LDL-c entry into cells.

4.2.3 Plasma high density lipoprotein:

In the current study feeding of 8% *sativum* fruits powder to an induced hypercholesterolemic Wistar albino rats caused a significant increase in HDL-c levels. These findings agree with Hwang *et al.* (2001) who concluded that supplementation of *sativum* whole fruits increase HDL-c levels due to the decreased production of VLDL, this is may be due to the fiber amount and omega 3 fatty acids content in the fruits. Also these findings agree with Chithra and Leelamma (1997) who concluded that supplementation of *sativum* fruits powder by oral intubation to rats increased HDL-c significantly but the mechanism is not well understood. Park *et al.* (2000) suggested that feeding of 5% fish oil to rats resulted in an increased HDL-c levels due to the inhibition of apo D activity which is responsible for the transferring of cholesteryl ester (CE) into VLDL. Murugaiah (1999) suggested that mixing of 35 and 70 mg of ginger with rats high fat diet increased HDL-c level significantly, this is may be due to the decreased production of VLDL. Tsang (2004) suggested that feeding of 5 % flax seeds to rats increased HDL-c levels and decreased the production of VLDL. However, feeding of 4% *sativum* fruits powder in this study did not affect the HDL-c concentration, which is in contrast to the finding of Ertas and Gular (2005). The non-significant increase in HDL-c level found in this study may be due to the short duration of the experiment.

According to what is mentioned above the increased HDL-c levels in this study may be due to the high fiber and high omega 3 fatty acids content in *sativum* fruits powder that reduce VLDL level

with a reduction in apo D activity that results in reducing the transfer of HDL-c to VLDL acceptors particles.

4.2.4 Plasma triglycerides:

The results showed that plasma triglycerides decreased significantly in the group treated with 8 % *sativum* fruits powder. These results agree with Hwang *et al.* (2001) and Chithra and Leelamma (1997), who reported that administration of *sativum* whole fruits or powder resulted in a significant decrease in the serum triglycerides level, which may be due to the fiber content that inhibits fatty acids synthesis. But feeding of 4% *sativum* fruits powder in this study showed no significant effect on triglycerides level, which may be due to the decreasing levels of fibers in this percentage or may be due to the short duration of the study. But these results disagree with Ertas and Guler (2005) who concluded that feeding of 4 % coriander whole seeds to quails for 5 weeks reduced significantly triglycerides concentration.

From the above mentioned results the mechanism by which *sativum* fruits powder reduces triglycerides level may be due to the high fibers content which have an effective role in reducing lipid synthesis as well as inhibition of fatty acids synthesis.

4.2.5 Plasma total lipid:

The results showed that the plasma total lipids level decreased significantly in the group treated with 8% *sativum* fruits powder. There is no scientific studies on the effect of *sativum* fruits on the total lipids level, but there are many medicinal plants which were used to reduce total lipids concentration. Prasanna (2000) reported that the administration of 5 % and 10% of fenugreek seeds added to rats basal diet resulted in a significant decrease in the serum total lipids level

this was attributed to the dietary fibers found in the plant which are responsible for the impairment of cholesterol absorption and reduction of fatty acids concentration. Judith and Samuel. (2005) concluded that feeding of 1.5 g of *Irvingia gabonensis* seeds added to rats basal diet 3 times a day for one month resulted in decreased serum total cholesterol as well as fatty acids synthesis, which may be due to the high fibers content in the plant. Sebokova *et al.* (1993) reported that administration of 30% omega 3 polyunsaturated fatty acids from fish oil mixed with rats diet for 14 days resulted in a significant reduction in serum total lipids and saturated fatty acids and this is due to the blockage of fatty acids synthesis. But feeding of 4 % *sativum* fruits powder in this study showed no effect on reducing total lipids levels which may be due to the low fibers and omega 3 fatty acids levels in this percentage or it may be due to the short period of the experiment.

According to the results mentioned above, the mechanism by which *sativum* fruits powder (8 %) reduced total lipids level may be due to the high fibers content and high amount of omega 3 fatty acids that suppress hepatic lipid synthesis as well as inhibition of the saturated fatty acids synthesis.

CONCLUSION

The results revealed that feeding of *sativum* fruits powder mixed diet significantly reduced plasma lipids profile in Wistar male albino rats when given at a dose of 8 % for one month.

Further work is suggested for the isolated hypolipidemic constituent(s) of this plant to elucidation of their mode of action.

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